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Epidemiology of sickle cell nephropathy in sickle cell anemia children, Saudi Arabia

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ABSTRACT

Background: Sickle Cell Nephropathy (SCN) is a group of renal abnormalities that developed in patients with Sickle Cell Disease (SCD). They begin early in the first decade of life and may progress to End Stage Renal Disease (ESRD) with increasing morbidity and mortality. *Methods:* The cross-sectional study included 484 SCD patients aged from one year to 15 years who had been admitted at Maternity and Children Hospital during the period from May 2009 to July 2019. eGFR was calculated by using the modified pediatric Schwartz equation. SCN was defined based on the presence of at least one of the following: Glomerular Hyperfiltration (GHF) when eGFR>140/ml/min/1.73m^2,Renal Insufficiency (RI) when eGFR <90 ml/ml/min/1.73m^2, or Renal Failure (RF) when eGFR<60ml/ml/min/1.73m^2. *Results*: Of the total 484 patients included in the analysis, 247 (51%) were females, 356 (73.6%) had HbSS genotype, 440 (91%) had at least one SCD related hospital admission, and 120 (24.8%) were on hydroxyurea therapy. About 24.8% of SCD patients had SCN as the following: 9.7% of them had GHF, 7.9% had RI, and 7.2% had RF. Patients with SCN were significantly had HbSS (p=0.027). *Conclusion*: About 24.8% of SCD patients had SCN as the following: 9.7% of them had GHF, 7.9% had RI, and 7.2% had RF. The prevalence of SCN was higher among patients with HbSS phenotype. Early detection of SCN could allow for earlier intervention and prevention of ESRD.

Keywords: Sickle Cell Nephropathy, Sickle Cell Disease

1. INTRODUCTION

Sickle Cell Disease (SCD) is one of the major global hemoglobinopathy (Mulumba & Wilson, 2015). It is a genetic condition that arises from a single point mutation in the β globin gene found on chromosome 11p15.4, leading to the replacement of glutamic acid of the β globin chain by valine resulting in an abnormal Hemoglobin S (HbS) molecule (Aloni et al., 2014; Olaniran et al., 2019). SCD may occur as a homozygous inheritance of HbS (HbSS), or even

quantitative mutations that result in decreased or absence of βglobin synthesis resulted in HbS-β thalassemia (HbSβ⁺) (Ephraim et al., 2015; Jastaniah, 2011). HbS causes Hb polymerization and abnormal red cell conformations, leading to chronic Red Blood Cells (RBCs) hemolysis, vessel occlusion, and ischemia-reperfusion injury, which leading to renal damage (Kimaro et al., 2019; Naik & Derebail, 2017).

Sickle Cell Nephropathy (SCN) is a well-defined group of renal abnormalities and occurs in up to one third of all patients (Brewin et al., 2017). The full pathophysiology of SCN is incompletely understood. However, the unique physiologic environment of the kidney leads to a susceptibility of renal injury in SCD. The acidic and hypoxic nature in the renal medulla predispose to RBCs sickling leading to vaso-occlusion, microinfarction, and ischemia. This ischemic change triggers the release of prostaglandins and nitric oxide leading to hyperfiltration and increase in the renal blood flow (Kimaro et al., 2019; Naik & Derebail, 2017; Halawani et al., 2020).

Gradual reduction in kidney function is common in SCD patients and begins early in childhood with impaired urinary concentration and glomerular hyperfiltration. Moreover, renal papillary necrosis, albuminuria, hematuria are eventually progress to End Stage Renal Disease (ESRD) which developed subsequently (Crosley & Strickland, 2005; Naik & Derebail, 2017; Elbalawy et al., 2019). Once patients with SCD progress to a GFR < 60 mL/min, the mean survival time is 4 years (Ephraim et al., 2015). Early screening and treatment of SCN in patients with SCD could help to reduce its prevalence.

2. METHODS

The cross-sectional study conducted at Maternity and Children Hospital (MCH). The study included patients with SCD aged from one year to 15 years of both genders during the period from May 2009 to July 2019. The electronic medical records were reviewed. A total of 850 children were identified to have a documented clinical diagnosis of SCD depend on Hb electrophoresis test result. Alkaline agar electrophoresis is the used method. Patients with 80-90% of HbS, 2-20% of HbF, and 2-3.4% of HbA2 were classified as HbSS, and those with HbA2 more than 3.4% were classified as HbSβ⁺.

Patients aged more than 15 years oldor with sickle cell trait (HbAS) were excluded. Patients with ESRD, urinary tract infections, or any systemic condition that could result in an RD not related to SCD (*e.g.*diabetes mellitus, hypertension, congenital anomalies in the kidneys) were excluded as well. Of the remaining 532 patients, we excluded 48 patients with missing serum creatinine levels, yielding 484 patients for this analysis (Figure 1).

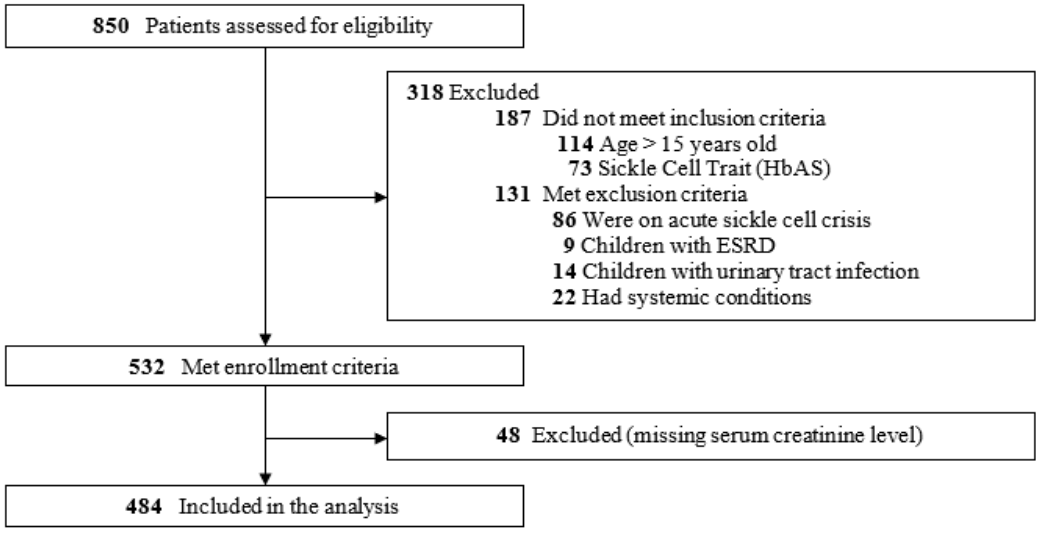

Figure 1 Study population flow chart

GFR estimation

We calculate the eGFR using the Modified Pediatric Schwartz Equation as follows:

Egrf (ml/min/1.73m²) = 0.413 x height (cm)/Serum creatinine (mg/dl)

The calculated eGFR was used to stratify the study population into stages of Chronic Kidney Disease (CKD) based on the staging system of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD (Löfman et al., 2016). SCN was defined

based on the presence of at least one of the following: Glomerular Hypertrophy (GHF) defined as eGFR>140/ml/min/1.73m^2, Renal Insufficiency (RI) defined as eGFR <90 ml/ml/min/1.73m^2, or Renal Failure (RF) defined as eGFR<60ml/ml/min/1.73m^2.

A high creatininelevel was defined as a serum concentration>70 μmol/L and high Blood Urea Nitrogen (BUN) level was defined as a serum concentration >4.6 mmol/L.Hb levels were categorized using the World Health Organization (WHO) classification of anemia severity as mild (Hb 10-10.9g/dl), moderate (Hb 7-9.9g/dl) and severe anemia (Hb <7g/dl) (Alraheili et al., 2020).

Demographic characteristics, SCD phenotypes, medical history, medications, laboratory parameters, and other clinical parameters were collected by reviewing the electronic medical records.

Ethical approval

The ethical committee board of MCH and the committee for research ethics on living creatures approved this study protocol (approval number: IRB00010219). All study parts were conforming to the declaration of Helsinki ethical principles for medical researches.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) software version 23. Continuous data are presented as median (minimum-maximum) as they were not normally distributed when tested by the Shapiro-Wilk test, while categorical data were presented as frequencies and percentages. Baseline demographic and clinical variables were compared between patients with SCN and without SCN using the Pearson Chi-Squared test for categorical variables. Mann-Whitney U test was used to assess whether the continuous variables differed among the study subgroups. P value ≤ 0.05 was considered significant.

3. RESULTS

Most of the patients aged between 5 to 15 years (Figure 2). Of the total 484 patients included in the analysis, 247 (51%) were females, 356 (73.6%) were HbSS, 440 (91%) had at least one of SCD related hospital admissions and 120 (24.8%) were on hydroxyurea therapy. According to WHO criteria of anemia, about 39 (8.1%) of SCD patients had mild anemia, 318 (65.7%) had moderate anemia, and 35 (7.2%) had severe anemia (Table 1).

Patients with SCN were significantly older. The median age of patients with SCN was 11 years old compared to 8 years old in patients without SCN (p=0.016). Patients with SCN were significantly had HbSS (p=0.027) (Figure 2) and SCD related hospital admissions (p <0.000). There was no significant association in gender (p=0.162). Also, there were no significant association in anemia (p=0.210), ischemic stroke (p=0.521), and hypersplenism (p=0.701). Other baseline clinical characteristics are displayed in (Table 2).

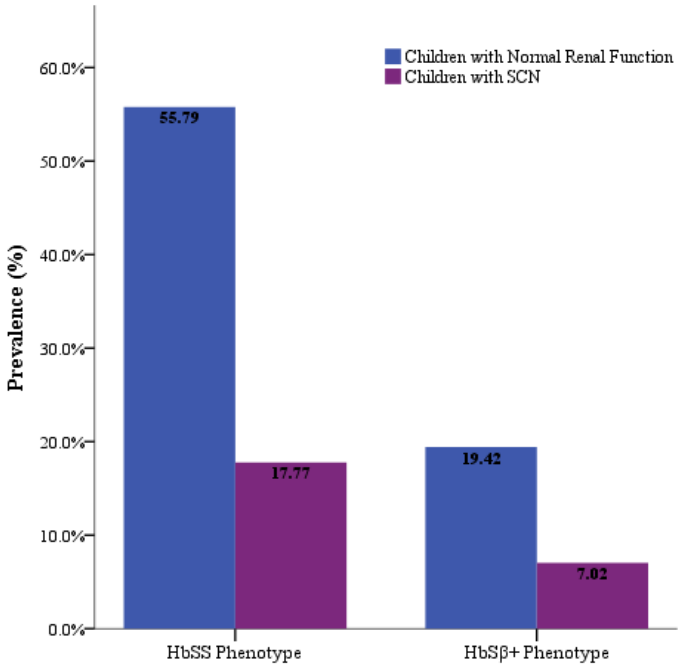

Figure 2 Prevalence of SCN regarding to SCD phenotypes

Table 1 Clinical characteristics of the study population		
Variables	(n=484)	(%)
Gender		
Male	237	(49.0)
Female	247	(51.0)
Age categories		
< 5 years	64	(13.2)
5 – 10 years	225	(46.5)
> 10 years	195	(40.3)
SCD phenotypes		
HbSS	356	(73.6)
HbSβ+	128	(26.4)
Medical history		
Acute chest syndrome	157	(32.4)
Hypersplenism	103	(21.3)
Ischemic stroke	23	(4.8)
SCD related hospital admissions	440	(91.0)
Severity of anemia		
No anemia (Hb > 11 g/dl)	92	(19.0)
Mild anemia (Hb 10–10.9g/dl)	39	(8.1)
Moderate anemia (Hb 7.0–9.9g/dl)	318	(65.7)
Severe anemia (Hb <7gldl)	35	(7.2)
Medications		
Hydroxyurea	120	(24.8)
Folic Acid	348	(71.9)
Ibuprofen	331	(68.4)
Penicillin	188	(38.8)
Paracetamol	299	(61.8)

Table 2 Clinical characteristics of 484 enrolled patients with SCD					
Variable	Normal Renal Function (n=364)(75.2%)		Sickle Cell Nephropathy (n=120)(24.8%)		*P* value
	Number (%) / Median (minimum-maximum)				
Age	8	(1-12)	11	(6-15)	0.016
Gender					
Male	170	(71.7)	67	(28.3)	0.162
Female	194	(78.5)	53	(21.5)	
SCD phenotypes					
HbSS	103	(28.3)	86	(71.7)	0.027
HbSβ+	94	(73.4)	34	(26.6)	
Medical history					
Acute Chest Syndrome	118	(75.6)	38	(24.4)	0.966
Hypersplenism	76	(73.8)	27	(26.2)	0.701
Ischemic Stroke	16	(69.6)	7	(30.4)	0.521
SCD related hospital admission	343	(78.0)	97	(22.0)	<0.000
Severity of anemia					

No anemia(Hb > 11 g/dl)	76	(82.6)	16	(17.4)	0.210
Mild anemia (Hb 10–10.9g/dl)	27	(69.2)	12	(30.8)	
Moderate anemia (Hb 7-9.9g/dl)	233	(73.3)	85	(26.7)	
Severe anemia (Hb <7gldl)	28	(80.0)	7	(20.0)	
Medications					
Hydroxyurea	296	(81.6)	22	(18.4)	0.014
Folic Acid	267	(76.6)	81	(23.3)	0.216
Ibuprofen	136	(37.5)	75	(62.5)	0.045
Penicillin	230	(76.9)	69	(23.1)	0.226

The use of medical therapy differed by the presence of SCN. Hydroxyurea using was decreased markedly in patients with SCN. Hydroxyurea was used in 18.4% of patients with SCN compared to 81.6% of patients without SCN (p=0.014). In addition, Ibuprofen using was higher in patients with SCN compared to patients without SCN. Ibuprofen was used in 62.5% and 37.5% in patients with SCN and without SCN, respectively (p=0.045); however, folic acid and penicillin use were not substantially different. All SCD patients had a similar hematological profile. The median Hb level was 9 g/dl. Lower median platelet counts 334×103/μL (range, 22-1287) was observed among patients with SCN in contrast to patients without SCN 410×103/μL (range, 5-1338) (p <0.000), although both of them were within the normal range. Regarding Hb electrophoresis analysis, median HbA% was 75 (range, 71-76) among patients with SCN compared to 80 (range, 80-97) of those without SCN (p <0.000). Median HbS% was 54 (range, 15-93) among patients with SCN compared to 48(range, 20-76) of those without SCN (p=0.026). There was a significant decrease in HbF% among patients with SCN. Median HbF% was 10 (range, 1.3-18) and 19 (range, 4.2-35) in patients with SCN and without SCN, respectively (p=0.002) (table 3).

Table 3 Biological profile of 484 enrolled patients with SCD

Variable	Normal Renal Function (n=364)(75.2%)		Sickle Cell Nephropathy (n=120)(24.8%)		*P* value
	Median (minimum-maximum)				
CBC					
Haemoglobin (g/dl)	9	(6-15)	9	(6-14)	0.836
HCT%	26	(16-46)	26	(16-41)	0.068
RBC $\times 10^{12}/\mu L$	3	(0-6)	3	(2-6)	0.342
MCV fL	80	(48-112)	86	(68-109)	0.059
WBC $\times 10^{3}/\mu L$	12	(0-32)	12	(1-70)	0.234
Platelet Count $\times 10^{3}/\mu L$	410	(5-1338)	334	(22-1287)	<0.000
Hbelectrophoresis					
HbA%	80	(80-97)	75	(71-76)	<0.000
HbA2%	4	(3-6)	3	(2-4)	0.125
HbF%	19	(4.2-35)	10	(1.3-18)	0.002
HbS%	48	(20-76)	54	(15-93)	0.026
Kidney function test					
eGFR	121	(95-140)	88	(14-694)	<0.000
Creatinine (μmol/L)	21	(13-74)	72	(10-490)	<0.000
BUN (mmol/L)	3	(1-14)	4	(1-44)	<0.000
Uric Acid (μmol/L)	208	(59-797)	242	(63-1172)	0.485
Electrolytes					
Sodium (mmol/L)	138	(129-151)	139	(130-160)	0.012

Potassium7(mmol/L)	4	(3-6)	4	(2-6)	0.083
Chloride (mmol/L)	104	(90-118)	105	(96-132)	0.064
Liver function tests					
AST (U/L)	41	(4-1095)	41	(12-370)	0.055
ALT (U/L)	22	(8-260)	27	(10-662)	<0.000
GGT (U/L)	21	(4-436)	16	(8-336)	0.015
Alkaline phosphatase (U/L)	180	(75-1015)	233	(72-519)	<0.000
Total Bilirubin (μmol/L)	30	(1-237)	35	(1-429)	0.005
Albumin (g/dl)	40	(15-50)	38	(22-51)	<0.000
LDH (U/L)	455	(142-1519)	484	(142-1916)	0.141
CBC, Complete blood count; HCT%, Hematocrit; RBC, Red Blood Cells; MCV, Mean Corpuscular Volume; WBC, White Blood Cells; BUN, Blood Urea Nitrogen; AST; Aspartate Aminotransferase, ALT;Alanine Aminotransferase.					

Patients with SCN exhibited significantly higher renal function tests. The median eGFR was higher in patients with SCN in contrast to patients without SCN (p <0.000), possibly due to include GHF stage one of the criteria of SCN. The median serum creatinine on admission was 72 μmol/L (range, 10-490) in patients with SCN in contrast to 21 μmol/L (range, 13-74) in patients without SCN (p <0.000). The median BUN level was 4 mmol/L (range, 1-44) and 3 mmol/L (range, 1-14) in patients with SCN and without SCN, respectively (p <0.000). In addition, the median uric acid was higher in patients with SCN in contrast to patients without SCN; however, no statistical significance was reached (p=0.485).

The median sodium level was slightly higher in patients with SCN. The median sodium level was 139 mmol/L (range, 130-160) in patients with SCN in contrast to 138 mmol/L (range, 129-151) in patients without SCN (p=0.012). In contrast to this, the levels of potassium and chloride on admission were not statistically different between the two groups. Moreover, liver function test showed that patients with SCN are more often exhibited low albumin levels, and a significantly higher levels of alanine aminotransferase (p <0.000), total bilirubin (p=0.005), and alkaline phosphatase (p <0.000). Median lactate dehydrogenase was higher in patients with SCN; however, no statistical significance was reached (p=0.141). Serum creatinine and height values were available to estimate GFR using the modified Schwartz equation in 484 patients. The overall prevalence of SCN among the study population was 24.8% defined bye GFR >140 or <90 ml/ml/min/1.73m^2. Thirty-eight (7.9%) of SCD patients met the definition for RI (eGFR89-60 ml/ml/min/1.73m^2) and thirty-five (7.2%) for RF (eGFR <60 ml/ml/min/1.73m^2). About 9.7% of SCD patients had CHF defined by (eGFR >140 ml/ml/min/1.73m^2) (Table 4).

Table 5 showed the prevalence of SCN according to SCD phenotype. The prevalence of GHF ranging from 9.4% in HbSB$^+$ to 9.8% in HbSS, but the prevalence of RI in HbSS (10.9%) wasslightly higher than HbSB$^+$ (6.7%). Also, RF was more in HbSS (7.6%) than the HbSB$^+$ (6.3%).

Table 4 Prevalence of SCN of 484 patients enrolled in the study

eGFR Categories	Number (%)
Normal Function (GFR 90–140)	364 (75.2)
Hyperfiltration (GFR >140)	47 (9.7)
Renal Insufficiency (GFR <90)	38 (7.9)
Renal Failure (GFR <60)	35 (7.2)

Table 5 Prevalence of SCN stratified by SCD phenotypes

eGFR Categories	HbSβ$^+$Thalassemia (n=128)	HbSS (n=356)
	Number (%)	
Normal function (GFR 90–140)	94 (73.4)	270 (75.8)
Hyperfiltration (GFR >140)	12 (9.4)	35 (9.8)
Renal insufficiency (GFR <90)	24 (6.7)	14 (10.9)
Renal failure (GFR <60)	8 (6.3)	27 (7.6)

4. DISCUSSION

Despite significant advances in the management of SCD and the presence of sophisticated medical provision, the proportion of patients progressing to SCN has consequently increased. The current study showed that the prevalence of SCN among SCD patients enrolled in the study is 24.8%. About 9.7% of patients with SCN had GHF, 7.9% had RI, and 7.2% had RF. Renal complications reported in 5-18% of SCD patients. In accordance with the results of the current study, a recent retrospective cohort study on 313 patients reported that 14.7% of them had SCN and majority of them were below 10 years of age (defined as eGFR<60ml/ml/min/1.73m^2). Similarly, a study conducted by Aloni et al., (2014) comparing kidney functions in 67 healthy children with 65 patients with SCD reported that 12.3% of patients with SCD had SCN (defined as eGFR<80ml/min/1.73m2). Moreover, a study done by Bodas et al., (2013) on 48 patients who followed at the rainbow babies and children's clinic found that about 8.3% of enrolled patients aged between 3 to 18 years had SCN.

A past study showed CKD was present in 50 out of 189 (26.5%) patients with SCD and it was more prevalent in adolescents (Yee et al., 2011). In addition, a recent study done by Kimaro et al., (2019) conducted in Tanzania enrolled 153 SCD patients with 3 months follow-up. They reported 20.3% of the patients had SCN (defined as eGFR <60ml/ml/min/1.73m2). They reported a higher prevalence of SCN in contrast to the current study findings most likely because of other prevalent conditions in Tanzania with the possibility to initiate renal damage such as severe malnutrition, malaria, urinary tract schistosomiasis, and HIV infection also, the time difference in the initiation of quality comprehensive SCD care. Moreover, the newborn screening at Saudi Arabia leading to early diagnosis and management with hydroxyurea therapy or chronic transfusion therapy is rarely at Tanzania.

In agreement with prior studies, the prevalence of patients with GHF in the current study was 9.7%. Similarly, Lakkakula et al., (2017) in a recent study found that 9.9% of SCD patients had GHF. However, previous studies reported a higher prevalence of GHF. Aloni et al., (2014) found that around 40% of SCD patients had GHF. Other studies reported that GHF has been observed in 70-98% of SCD patients (Aygun et al., 2011; Aloni et al., 2017). The discrepancy in the prevalence of GHF between studies could be attributed to the difference in age, genetics and environmental factors, ethnicity, as well as the differences in methods used to estimates GFR and cut-off values for defining GHF. Older age, number of SCD related hospital admissions, ibuprofen use, and HbSS were associated with a higher prevalence of SCN. In contrast to the current study, Christopher in a past descriptive cross-sectional study conducted at Tanzania included 120 children and adolescents aged 3 to 18 years attending sickle cell clinic reported that low Hb level was associated with SCN (Lakkakula et al., 2017).

It is still unknown about the role of low Hb level on the worsening of kidney functions among SCD patients. It may be explained that SCN leading to decrease the erythropoietin level causing decrease the number of the circulating RBCs and oxygen carrying capacity, along with increase in the HbS polymerization in the renal medulla which accentuation the renal damage (Kimaro et al., 2019). However, in the current study, no differences were found regarding Hb level. A prospective study done by Aygun et al., (2013) revealed a beneficial effect of hydroxyurea use by decreasing the incidence of GHF which may affect the progression of GHF to renal dysfunction. Similarly, this study had shown that hydroxyurea use had a protective effect against SCN.

Moreover, we observed a significantly high prevalence of SCN in HbSS patients compared to HbSβ patients. The prevalence of RI in HbSS (10.9%) was slightly higher than HbSB$^+$ (6.7%). Further, RF was more in HbSS (7.6%) than the HbSB$^+$ (6.3%). The higher concentrations of HbF and HbA2 in patients with HbSB$^+$ may contribute to less hemolysis and vaso-occlusion in these patients. Also, patients with HbSB$^+$ tend to have fewer and less severe acute complications, chronic organ damage, including renal damage.

5. CONCLUSION

The prevalence of SCN among patients with SCD was 24.8%. About 9.7% of patients had glomerular hyperfiltration, 7.9% had renal insufficiency, and 7.2% had renal failure. Most of the patients with SCN had HbSS phenotype.

Informed consent

Oral informed consent was obtained from all individual participants included in the study.

Ethical approval

The standing committee for research ethics on living creatures and the ethical committee board of MCH approved this study protocol (approval number: IRB00010219).

Author's contributions

All authors contributed to the research and/or preparation of the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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Data and materials availability

All data associated with this study are present in the paper.

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